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Docket No. A018 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Gotwals, et al.
Application No.: 09/423,018 Group Art Unit: 1646
Filed: October 12, 2000 Examiner: Janet Andres Ph. D.
Title: TYPE II TGF-BETA RECEPTOR/IMMUNOGLOBULIN CONSTANT
REGION FUSION PROTEINS

Commissioner for Patents
Washington, D.C. 20231

Cons. L. 4/15/03

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DECLARATION OF PHILIP GOTWALS, Ph. D

TECH CENTER 1600/2900

Philip Gotwals, Ph. D. declares and states as follows.

1. I am an inventor named in the above-identified United States Patent Application Serial No. 09/423,018 (the "Application") and I am familiar with the contents of the Application, including claims 1-4, 6, 7, and 10 ("Claims"). I have also reviewed and am familiar with: (1) the July 30, 2002 Office Action issued by the United States Patent and Trademark Office in connection with the Application; (2) *Massague* (*Ann. Rev. Biochem.* 1998, vol. 67, pp. 753-791) ("*Massague*") cited by the Examiner in the July 30, 2002 Office Action in support of her rejection of claims 1-3 and 10 ("Claims") of the Application as being unpatentable as nonenabled; and (3) U.S. Patent No. 6,046,157 ("*Lin*") and U.S. Patent No. 5,605,690 ("*Jacobs*"), cited by the Examiner in support of her rejections of the Claims as being unpatentable as obvious.

2. Those of skill in the art as of the effective filing, with the disclosure of the Application, could have, without undue experimentation, naturally derived, recombinantly expressed, or synthetically made an amino acid sequence at least 60%, 80%, 90%, 95%, 98%, or 99% homologous to an amino acid sequence from SEQ ID

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NOS: 8 or 9 of the Application. Without undue experimentation, and with the disclosure of the Application, they could have applied the signal transduction techniques disclosed in the Application to determine if proteins comprising such sequences inhibited binding of TGF-beta to a TGF-beta receptor. And as described in the following section, those of ordinary skill in the art, from the disclosure of the Application, would have been able to identify the fusion partners for such sequences described in the fusion proteins of the Claims.

3. The Application discloses at page 26, lines 18-20; that "[s]pecifically, the second protein may be the constant region of an immunoglobulin (preferably IgG, most preferably IgG1) or may be a portion thereof such as the hinge, C_H2 or C_H3." Those of ordinary skill in the art as of the effective filing date could have, in light of the disclosure of the Application and without undue experimentation, identified and isolated such immunoglobulin regions or portions thereof without undue experimentation for use as fusion partners.

4. *Massague* describes the variety in ligand binding of TGF- β receptors I and II, but provides no basis to suggest that TGF- β fusion proteins comprising amino acid sequences of the homology previously described and constant regions of an immunoglobulin (preferably IgG, most preferably IgG1) or a portion thereof such as the hinge, C_H2 or C_H3, will not inhibit binding of TGF- β to a TGF- β receptor as defined in the Application. In fact, the *Lin* patent notes that a common functionality of TGF- β I and II receptors has been suggested (column 7, lines 14-17).

5. *Lin* lacks any teaching of fusion proteins like those of the Claims. *Lin* simply describes the DNA sequences encoding TGF- β II and III receptors and the expression and characterization of encoded products. *Lin* states that TGF- β II and III receptors

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encoded by the receptor genes of *Lin*'s invention can be used as both agonists and antagonists to alter the effect of TGF- β *in vivo*. (*Lin*, column 7, lines 63-67; column 8, lines 1-7). *Jacobs* describes TNFR/Fc fusion proteins comprising a single molecule of soluble TNFR linked to a single chain of Fc derived from human IgG1. There is no suggestion in *Jacobs* that TNFR are in any way "analogous" to TGF- β R. The DNA sequences and related compositions of *Jacobs* are wholly distinct from those of the Claims. The knowledge of those of ordinary skill in the art at the time the invention of the Claims was made would not have suggested combining *Lin* and *Jacobs* to make the claimed invention.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on the basis of information and belief are believed to be true, and further that these statements have been made with the knowledge that willful false statements so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such false statements may affect the enforceability of any patent claims issuing in connection with the Application.

By: Philip Gotwals

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